Remarks

By this amendment, claims 6, 10 and 11 have been amended. Accordingly, claims 1-6, 8-11, and 13-16 are currently pending in the application, of which claims 1, 9, and 14 are independent claims.

Entry of the Amendments and Remarks is respectfully requested because entry of Amendment places the present application in *prima facie* condition for allowance, or in the alternative, better form for appeal. Applicants respectfully submit that the above amendments do not add new matter to the application and are fully supported by the specification. Applicants further submit that no issues requiring a further search are presented.

In view of the above amendments and the following Remarks, Applicants respectfully request reconsideration and timely withdrawal of the pending objections and rejections for the reasons discussed below.

Rejections Under 35 U.S.C. §102

Claims 1-4, 6, 8-11 and 13-16 stand rejected under 35 U.S.C. §102 as being anticipated upon a public use or sale of the invention based on breast-feeding. The Examiner takes the position that leptin is naturally administered orally to infants who are breast fed and who may be premature and have impaired surfactant production and respiratory distress syndrome or Bronchopulmonary Dysplasia. The Examiner indicated that the levels of leptin in premature milk are still within the ranges of claims 6 and 11. Applicants respectfully traverse this rejection for at least the following reasons.

As Applicants have maintained, the leptin levels in premature breast milk are not sufficient to enhance surfactant production in an individual as claimed in claims 1, 9, and 14. The leptin levels measured in Applicant's publication were measured in established breast milk in which the mother delivered full-term infants, not premature infants. Importantly, the level of leptin in premature breast milk is significantly lower than leptin levels in established breast milk. Resto et al. (2001) reported leptin levels in premature breast milk as 5.28+/- 24.79 compared to the levels reported in established breast milk 73.22 +/- 39.08. This data coupled with the finding that small-for gestational age infants show only a marginal increase (23%) in serum leptin levels after breast feeding, whereas appropriate-for-gestational age and large-for-gestational age infants demonstrate much larger increases of 47% and 136%, respectively (Cinaz et al., 1999) leads to the conclusion that when a mother breast feeds a premature infant, the mother's premature breast milk *does not have* sufficient leptin levels that would amount to administering a leptin compound to the individual for a time and in an amount sufficient to enhance surfactant production as required in claims 1, 9, and 14. This conclusion is substantiated by the study of Spear et al. (2001) in which it is shown that serum leptin levels are low in premature infants and remain low during the duration of the premature infants' hospitalization despite adequate nutrition, including breast feeding.

The Examiner references that the levels of leptin in premature milk are 26 times the required amount of leptin within the ranges of claims 6 and 11. The Examiner is comparing a concentration of 5.28ng/ml with the claimed amount of 0.1ng/kg of body weight. A direct comparison between a concentration measurement and an amount per body weight cannot be made and is not a proper comparison. To sustain this comparison several assumptions would have to be made. The initial assumption is the unlikely event that a premature infant is in fact

able to successfully breast feed. The above comparison further assumes that the mother could provide premature breast milk. Next, an assumption would have to be made about the amount of premature breast milk that would be able to be fed to the premature infant. Even if all these events were likely, the claims require an amount of leptin sufficient to enhance surfactant production and as discussed above, the provided references clearly teach that premature breast milk does not have sufficient leptin levels to enhance surfactant production. Applicants have amended claims 6 and 11 to require 10ng/kg of body weight.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §102 rejection of claims 1-4, 6, 8-11 and 13-16. Since none of the other prior art of record discloses or suggests all the features of the claimed invention, Applicants respectfully submit that independent claims 1, 9, and 14, and all the claims that depend therefrom are allowable.

Rejections Under 35 U.S.C. §103

Claims 1-6, 8-11 and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Torday et al., FASEB Journal, March 15, 2000, Vol. 14, No. 4, and/or Torday et al., Pediatric Research, 378A, March 2000, and further in view of Griese, European Respiratory, Journal, 1999, and Halliday et al., In: Hot Topics in Neonatology, 1999, and O'Donnell et al., Am. J. Resp. Crit. Care Med 159, 1999.

The Examiner had indicated that upon submission of the reference from the previous response, the rejection would be reconsidered. Applicants have provided these references and maintained that claims 1-6, 8-11 and 13-16 are not obvious. The Examiner takes the position that it would have been prima *facie obvious* to increase the production of lung surfactant in respiratory conditions in which individuals have impaired surfactant production, by treatment

with leptin, as taught by Torday et al., because Halliday teaches that treatment with corticosteroids has not been proven effective and has serious side effects, and because Griese teaches that there are a number of respiratory diseases in which lung surfactant is deficient and needs to be enhanced or replaced. The Examiner further contends that there would be a reasonable expectation of success, since O'Donnell et al. teaches enhancement of respiratory function by exogenous treatment with leptin, though the mechanism of enhancement was not known.

First, as pointed out by the Examiner, Griese and Halliday et al. show a need for alternative treatments to increasing lung surfactant production. However, these references do not show, teach or suggest that administering leptin to an individual will *enhance surfactant production* in an individual as required by claims 1, 9, and 14.

Turning now to the O'Donnell et al. reference, O'Donnell et al. show that leptin acts centrally at the level of hypothalamic control centers in the brain to control respiration and ventilation. Importantly, there is no evidence for leptin acting peripherally on other tissues, like lung tissues, to control respiratory function. Further, O'Donnell did not examine the effects of leptin on immature lung tissue as seen in premature infants with RDS nor in adults with insufficient or low surfactant levels as found in adult cases with RDS. Accordingly, O'Donnell does not disclose, teach or suggest that leptin may be administered to an individual to *enhance surfactant production* as required by claims 1, 9, and 14.

This deficiency is not cured by the Torday et al. references. Torday et al. show that leptin increases phosphatidylcholine levels in an established lung cell line. They do not show that leptin increases the levels of surfactant proteins A, B, and C. Further, they do not demonstrate that leptin increases phosphatidylcholine levels in an animal model nor in lung cells or tissue with

insufficient production of surfactant as would be found in premature infants with RDS or in adults with ARDS. Furthermore, it has been demonstrated that the genes encoding the surfactant proteins are regulated independently from each other and from the genes responsible for regulating phospholipid synthesis (Mendelson and Boggaram, 1991; Rooney, Young, and Mendelson, 1994; Whitsett et al., 1995). For example, insulin has been shown to increase phospholipid production, yet decrease the levels of surfactant protein A and increase the incidence of RDS. In addition, animal models in which the surfactant proteins have been knocked out all demonstrate RDS and fail to survive. Also, surfactant preparations that lack the surfactant proteins are more efficacious in the prevention and treatment of RDS in prematurely born infants than are the synthetic phospholipids mixtures. Neither Torday et al. or O'Donnell et al. either alone or in combination, discloses, teach, or suggest that leptin may be administered to an individual to enhance lung surfactant production as required by claims 1, 4, and 9.

Accordingly, Applicant respectfully contends that claims 1, 4, and 9 are not obvious over Torday et al., Griese, Halliday et al., or O'Donnell et al. either alone or in combination with one another. Claims 2-6, 8, 10-11, 13, and 15-16 are dependent claims that depend from either claim 1, 9, or 14 and are likewise not obvious over Torday et al., Griese, Halliday et al., or O'Donnell et al.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §103(a) rejection of claims 1-6, 8-11 and 13-16. Since none of the other prior art of record, whether taken alone or in any combination, discloses or suggests all the features of the claimed invention, Applicants respectfully submit that independent claims 1, 9, 14, and all the claims that depend therefrom are allowable.

Copies of all of the references discussed above are provided in Exhibit A, attached to this response.

CONCLUSION

Applicants believe that a full and complete response has been made to the pending Office Action and respectfully submit that all of the stated objections and grounds for rejection have been overcome or rendered moot. Accordingly, Applicants respectfully submit that all pending claims are allowable and that the application is in condition for allowance.

Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the Applicant's undersigned representative at the number below to expedite prosecution.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

Philip D. Lane, Ph.D.
Reg. No. 41,140

Date: August 25, 2003

McGuireWoods LLP
1750 Tysons Boulevard
Suite 1800
McLean, VA 22102-4215
Tel: 703-712-5069
Fax: 703-712-5296